Remarks

Claims 1-6, 8, 22, and 24-40 are pending in the subject application. By this Amendment, Applicants have amended claims 1 and 6. Support for the amendments can be found throughout the subject specification and in the claims as originally filed. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1-6, 8, 22 and 24-40 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

At the outset, Applicants request the courtesy of an interview in this matter prior to the issuance of an Advisory Action in this matter.

Applicants gratefully acknowledge the Examiner's withdrawal of the objection to claim 6 and certain of the rejections under 35 U.S.C. § 112, second paragraph, the rejection over 35 U.S.C. § 103(a) (over Aebersold *et al.*).

Claims 1-6, 8, 22 and 24-40 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Applicants respectfully assert that the claims as filed are definite. The Office Action indicates that it is unclear what "A", "Y" and "PRG" refer to in claims 1b and 6. Applicants have amended the claims in accordance with the Examiner's suggestion and request reconsideration and withdrawal of this rejection.

Claims 1-6, 8, 22 and 24-38 remain rejected under 35 U.S.C. § 103(a) as obvious over Aebersold *et al.* (WO 00/11208) in view of Moutiez *et al.* (1997) and Li *et al.* (1997). The Office Action states that if Aebersold *et al.* were to teach a metal labeled reagent, they would anticipate applicants' invention. However as explained above, other references teach the advantages of using metal ion labeled reagent. The Office Action reiterates that Li *et al.* teach a well characterized spectra of peptide bound silver ion in mass spectral analysis. The Office Action notes that it is well known in the art the advantage of purifying and detecting proteins using chelated metal tags comprising various metal ions using a variety of chelating agents, such as lanthanide metal ions. Therefore in order to identify and quantify proteins in proteomic samples, one of ordinary skill in the art is motivated to modify the A-L-PRG of Aebersold *et al.* with Gd^{3+} DOTA chelate not being modified by isotope label and use the metal ion as standard (as taught by Li *et al.*) in the method of Aebersold *et al.* because a peptide sample attached to L-PRG with Gd^{3+} DOTA can be separated by

metal ion chelate affinity column by HPLC, and optionally can be detected by luminescence before passing into the mass spectrometer. Thus, the claimed invention remains *prima facie* obvious over the prior art of record. Applicants respectfully assert that the claimed invention is not obvious over the cited references.

Aebersold *et al.* describe isotope coded affinity tag (ICAT) technology. As discussed in the as-filed specification (see page 4, line 18 through page 5, line 27), ICAT technology relies on (and requires) the use of isotopes in order to allow for the quantification and identification of biological molecules labeled via ICAT technology. As described in the as-filed specification, the ICAT technology is fundamentally different from the present invention (and thus is not similar).

While Aebersold *et al.* employ affinity tagged protein reactive reagents in which the affinity tag is covalently attached to a protein reactive group by a linker (*i.e.*, A-L-PRG), the linker (L) is isotopically labeled to generate pairs or sets of reagents that are substantially chemically identical, but which are distinguishable by mass because of the isotopic labeling. Aebersold *et al.*, beginning in the paragraph bridging pages 13-14, discuss the structure of L, and state that "*at least some of the atoms of L should be readily replaceable with stable heavy atom-isotopes*", *i.e.*, the label (or tag) actually used by Aebersold *et al.* Aebersold *et al.* then further state: "*The linker preferably contains groups or moieties that facilitate ionization of the affinity tagged reagents, peptides, substrates or reaction products.*" (emphasis added). Therefore, the groups as discussed are exclusively added to facilitate ionization of the molecules (irrespective of their actual tag, namely, the isotope label). This is why the next sentences in paragraph 2 on page 14 read:

> *To promote ionization, the linker may contain [...]. The linker may also contain groups having a permanent charge, e.g., phosphonium groups, quaternary ammonium groups, sulfonium groups, chelated metal ions, tetralky or tetraryl borate or stable carbanions.*" (emphasis added)

Thus, the chelated and permanently charged metals are used for ionization in the MS-analysis, but do not, and actually must not, provide a mass difference.

As noted previously, if a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 U.S.P.Q. 1125 (Fed. Cir. 1984). In this

case, the modification to the teachings of Aebersold *et al.* proposed in the Office Action renders the prior art invention unsatisfactory for the analysis of proteins. As noted in the previous response, the present invention differs from the disclosure of Aebersold *et al.* in that the claimed method does not utilize isotopically labeled reagents for the identification of labeled peptides (*i.e.*, the reagent of general formula A-Y-PRG is not isotopically labeled). Indeed, the claims require that the reagent is not isotopically labeled. Thus, modification of the reference such that it does not utilize an isotopically labeled reagent would render it unsuitable for its use in the teachings of Aebersold *et al.* and there would have been no motivation to modify the teachings of Aebersold *et al.* as proposed in the Office Action.

It is fundamental patent law that an obviousness rejection fails if the prior art relied on does not disclose all of the limitations of the claimed invention. *See, e.g., In re Zurko*, 258 F.3d 1379, 1385-86 (Fed. Cir. 2001). Thus, obviousness requires a teaching or suggestion of all limitations in a claim. *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (C.C.P.A. 1974)). In this case, Applicants also submit that the obviousness rejection of record fails to teach each of the limitations of the claimed invention. As noted above, Aebersold *et al.* **requires** the use of isotopically labeled reagents in order to quantify and identify biological molecules to which the reagent has been attached. As also noted above, the claimed invention utilizes reagents that **are not** isotopically labeled. Thus, the combined teachings of cited references fails to teach each of the limitations of the claimed invention and a *prima facie* case of obviousness has not been established.

A fact finder should be aware of the distortion caused by hindsight bias. *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1742 (2007) and "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 127 S.Ct at 1741. Applicants further submit that the rejection of record amounts to hindsight reconstruction of the claimed invention. To use chelated metal ions (and no isotopes) as argued in the Office Action is neither disclosed nor proposed by Aebersold *et al.* In fact, Aebersold *et al.*'s actual analysis is based on the use of "integrated" isotopes in the reagents used in the methods disclosed therein. Thus, in order to arrive at the present invention, starting from Aebersold *et al.*, the person of skill had to:

1) disregard the main technical feature of Aebersold *et al.*, namely the isotope tagging of biological molecules (without a chelator being involved),

2) add and permanently include a chelator into the L-group of Aebersold *et al.*, and

3) include a lanthanide metal ion as the label.

There is no motivation in Aebersold *et al.* to modify the A-L-PRG-affinity tagged protein reactive reagents in *any* of the three ways as described above at 1) to 3) nor do any of the additional references suggest modification of Aebersold *et al.* in such a fashion. The Office Action refers to Porath *et al.* and Moutiez *et al.* with the statement that "the advantage of using chelated metal tags comprising various metal ions would be well known in the art when purifying and detecting proteins", and construes a motivation of the person of skill to combine these references with Aebersold *et al.* Moutiez *et al.* describes a completely different technology, namely, metal chelate chromatography. Moutiez *et al.* uses the chelate complexes in order to create "a rapid, simple and sensitive RP-HPLC method for detecting Gd-DOTA and revealing free Gd^{3+} in samples" (see section "conclusion"). This is then coupled with luminescence ("TRL"). Using this technology, 130 ng of Gd3+ ion can be detected in samples (see abstract, at the end). Even if one would try to use the chelate affinity chromatography for a separation of individual MeCAT-labeled peptides according to the invention from a mixture of peptides, the separation characteristics would be insufficient, and thus – as the person of skill is absolutely aware – this method cannot be used.

Moutiez *et al.* explicitly indicated that the method disclosed in the reference is less sensitive than MS techniques used to quantify Gd content in samples, and thus explicitly teach away from using this technique as argued in the Office Action: "In comparison with more sensitive methods used to quantify total Gd (ICP-MS) […]"(see section "conclusion" lower third; ICP-MS = inductively-coupled-plasma mass-spectrometry). "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley,* 27 F.3d 551, 553 (Fed.Cir.1994); *see KSR Int'l Co. v. Teleflex Inc.,* 127 S.Ct. 1727, 1739-40 (explaining that when the prior art teaches away from a combination, that combination is more likely to be nonobvious). Thus, it is respectfully submitted that one skilled in the art would not have been motivated to proceed as argued in the Office Action; rather, one would

have been lead in a direction divergent from that taken by Applicants in this matter. Accordingly, reconsideration and withdrawal of the rejection of record is respectfully requested.

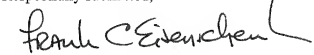
It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

FCE/sl